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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
FREDMAN, JEFFREY NORMAN	
ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 05/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/829,113	EVANS ET AL.	
	Examiner	Art Unit	
	Jeffrey Fredman	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 October 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18,21 and 22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18,21 and 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on March 22, 2004 has been entered.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

4. Claims 1-16, 21 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Li et al (Biotechniques (1998) 25(3): 358, 360, 361) in view of Patel et al (Nucleic Acids Research (1991) 19:3561-3567) and further in view of Michalatos-Beloin et al (Nucleic Acids Res. (1996) 24:4841-4843).

Li teaches a method of determining the haplotype structure of a contiguous DNA segment comprising a first nucleotide polymorphism and a second nucleotide polymorphism (see page 360, figure 1) comprising:

(a) obtaining a DNA sample from a human source comprising said contiguous DNA segment (page 358, column 1),

(b) using said DNA sample as a template for polymerase chain reaction amplification of a DNA fragment to form a product which is capable of being subject to intramolecular ligation (page 358, column 2, subheadings "GPA-specific PCR" and page 360, figure 1),

wherein the PCR amplification is performed with

(i) a first primer capable of annealing to a region adjacent to the first NP and distal to the second NPs (see figure 1, where the MN-FP primer is adjacent to the 5'G/T polymorphism and distal from the 3' G/T, C/A/G and C/T polymorphisms)

(ii) a second primer capable of annealing to a region adjacent to the second NP and distal to the first NP (see figure 1, where the MN-CR primer is adjacent to the 3' G/T, C/A/G and C/T polymorphisms and distal from the 5' G/T polymorphism),

(c) ligating the ends of the DNA fragment to each other so as to produce a circular DNA molecule (page 358, subheading "ligation of the amplified fragment" and

page 360, figure 1), wherein the ligation brings the first and second polymorphisms into closer proximity on the circular DNA molecule (see figure 1, page 360 and page 361, column 1, which states "ASIP rather than nested PCR, can be applied to haplotyping of polymorphisms separated by a distance that is too long to be amplified by PCR"),

(d) determining the haplotype of the first and second nucleotide polymorphism by allele specific inverse PCR amplification (page 358, subheading "Allele specific PCR" and page 360, figure 1).

With regard to claims 5-8, Li teaches first, second and third NPs that are single nucleotide substitutions with some NPs located between the end NPs whose haplotype is determined (see figure 1, page 360).

With regard to claim 9, Li teaches use of human sources (see page 358, column 1).

With regard to claim 13, Li teaches that the primers are allele specific (see page 360, figure 1).

With regard to claims 14-16, Li teaches determination of each allele of the clinically relevant Glycophorin gene (see page 358, column 1 and page 360, figure 1).

With regard to claims 21 and 22, Li teaches a DNA sequence immediately adjacent to the 5' and 3' NPs which is less than 50 bases long.

Li suggests the use of the method on haplotyping distances that are too long to be PCR amplified (see page 361, column 1).

While Li suggests applying the method to situations with polymorphisms that are distant from one another, Li does not exemplify application of the method to sequences which are 200 to 30,000 bases apart nor the use of long range PCR.

Regarding claim 1 and dependent claims 2-4, Patel teaches that inverse PCR methods such as those used by Li can be applied to haplotype sequences up to 10 kb apart and suggests that even larger regions can be used (page 3567, column 1, lines 6-9).

Regarding claims 11 and 12, Patel teaches restriction digestion to enhance inverse PCR and detection with such digestion (see page 3562, column 1 and page 3563, figure 2)

Patel teaches mutations which are substitutions of single nucleotides and where there are a series of nucleotide polymorpisms located between the two amplified polymorphisms (see page 3561, column 2 and page 3562, figure 1). Patel teaches determing the presence of multiple different polymorphisms (see page 3565, column 1, subheading "Double ARMS Inverse PCR (DARMSI-PCR)". Patel teaches amplification and detection of each haplotype in the same gene, the globin cluster (page 3562, figure 1). Patel further teaches that the method can be used for diagnostic purposes (see page 3567, column 1).

Michalatos-Beloin teaches haplotyping methods where the molecules are prepared by long range PCR (page 4842, figures 2 and 3). Michalatos-Beloin also teaches that amplification of up to 40 kb should be possible (see page 4843 (listed as page 4867), column 2).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to utilize the long range PCR method of Michalatos-Beloin to amplify the sample of Li since Michalatos-Beloin states "The allele-specific long range PCR products were used as templates for amplification of the STR (page 4867, column 1)". An ordinary practitioner would have been motivated to use long range PCR to prepare the template for the method of Li in order to extend the range of detection of polymorphisms in order to solve the problem of Li that there are "polymorphisms separated by a distance that is too long to be amplified by PCR (see page 361, column 1)." Li recognizes the problem in that some haplotypes are too distant to be amplified by standard PCR. Michalatos-Beloin solves the problem using long range PCR. Further, Michalatos-Beloin notes "The ability to isolate hemizygous DNA segments readily from heterozygous genomes via molecular haplotyping will provide the accuracy necessary in these diverse applications (page 4867, column 2). Thus, application of the method of Michalatos-Beloin to the inverse PCR method of Li can be used to increase the accuracy of the Li method. Further motivation to apply the Michalatos-Beloin method to Li is provided by Patel, who teaches that haplotyping using inverse PCR is desirable on long segments, even haplotypes separated by more than 10,000 nucleotides (see page 3567, column 1). This represents further motivation to apply the method of Li to more widely separated polymorphisms, as well as teachings on how to perform that method.

5. Claim 17 is rejected under 35 U.S.C. 103(a) as being unpatentable over Li et al (Biotechniques (1998) 25(3): 358, 360, 361) in view of Patel et al (Nucleic Acids

Research (1991) 19:3561-3567) in view of Michalatos-Beloin et al (Nucleic Acids Res. (1996) 24:4841-4843) as applied to claims 1-16, 21 and 22 and further in view of Krynetski et al (Proc. Natl. Acad. Sci. (1995) 92:949-953).

Li et al (Biotechniques (1998) 25(3): 358, 360, 361) in view of Patel in view of Michalatos-Beloin teach the limitations of claims 1-16, 21 and 22 as discussed above. Li et al (Biotechniques (1998) 25(3): 358, 360, 361) in view of Patel in view of Michalatos-Beloin do not teach application of the method to the TPMT gene.

Krynetski teaches that there are two haplotypes in the TPMT gene, one of which is associated with cytotoxicity in chemotherapeutic treatment using methylmercaptopurine (see page 949, columns 1 and 2).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to utilize the method of Li et al (Biotechniques (1998) 25(3): 358, 360, 361) in view of Patel in view of Michalatos-Beloin to haplotype the TPMT gene since Krynetski teaches "Identification of the inactivating mutations at the TPMT locus would not only provide important insights into the molecular mechanisms of this genetic polymorphism but might also offer a method of prospectively identifying heterozygotes and TPMT-deficient patients prior to treatment with potentially toxic dosages of mercaptopurine (page 949, column 2)". Thus, an ordinary practitioner would have been motivated to haplotype the TPMT gene using the method of Patel in view of Michalatos-Beloin, where Patel teaches that the method is useful "for routine diagnostic purposes (page 3567, column 1)", in order to diagnose patients who are TPMT deficient prior to toxic treatment.

6. Claim 18 is rejected under 35 U.S.C. 103(a) as being unpatentable over Li et al (Biotechniques (1998) 25(3): 358, 360, 361) in view of Patel et al (Nucleic Acids Research (1991) 19:3561-3567) in view of Michalatos-Beloin et al (Nucleic Acids Res. (1996) 24:4841-4843) as applied to claims 1-16, 21 and 22 and further in view of Martin et al (Am. J. Hum. Genet. (2000) 67:383-394).

Li et al (Biotechniques (1998) 25(3): 358, 360, 361) in view of Patel in view of Michalatos-Beloin teach the limitations of claims 1-16, 21 and 22 as discussed above: Li et al (Biotechniques (1998) 25(3): 358, 360, 361) in view of Patel in view of Michalatos-Beloin do not teach application of the method to the listed genes.

Martin teaches haplotype analysis of the ApoE gene in order to analyze the presence of Alzheimer's disease (abstract).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to utilize the method of Li et al (Biotechniques (1998) 25(3): 358, 360, 361) in view of Patel in view of Michalatos-Beloin to haplotype the ApoE gene since Martini teaches "Haplotype analysis using family data increased significance over that see in single-locus tests for some of the markers, and for these data, improved localization of the gene (abstract)." Thus, an ordinary practitioner would have been motivated to haplotype the ApoE gene using the method of Patel in view of Michalatos-Beloin, where Patel teaches that the method is useful "for routine diagnostic purposes (page 3567, column 1)", in order to diagnose patients who are at risk for Alzheimer's disease.

Response to Declaration

7. The Declaration under 37 CFR 1.132 filed March 22, 2004 is insufficient to overcome the rejection of the claims based upon 35 U.S.C. 103(a) as set forth in the last Office action because:

The Declaration begins by performing a piecemeal analysis of the references, in particular pointing out that each reference does not anticipate the claims, but rather lacks some element of the claimed invention. These statements are correct. Since the rejection proposed was under 35 U.S.C. 103, it is clear that the references were not proposed to anticipate the invention and the references necessarily differed from the claimed invention. These initial statements fail to address the heart of the issue in the rejection, which is whether the invention is prima facie obvious over the combination of the Li, Patel and Michalatos-Beloin.

The Declaration then states that Li does not circularize to bring the polymorphisms closer together. This is not correct. Li states "Although these alleles can be typed by allele specific nested PCR following GPA-specific PCR, ASIP, rather than nested PCR, can be applied to haplotyping of polymorphisms separated by a distance that is too long to be amplified by PCR (see page 361, column 1, paragraph 1)."

Contrary to the Declarant's statement, this is an express statement to perform the intent of the invention. Li is clearly indicating that in his example, nested PCR would have worked. Li then expressly suggests that where polymorphisms are too far apart for nested PCR, ASIP should be applied. ASIP is functionally identical to Applicant's

invention, except for the requirements that there be a separation of 200, 1000, 10,000 or 30,000 nucleotides. In the cited portion of Li, Li clearly intends suggests the application of the ASIP method to polymorphisms to far apart to be amplified by PCR.

The Declarant, on page 4, then attempts to place the quote in a context which is not correct because it ignores and distorts the plain meaning of Li. Li would not have said that the 30-40 bases between the polymorphisms was a distance too long to be amplified by PCR when he amplified a 357 base pair fragment. Consequently, Li must have been referring, in his quote, to other polymorphisms which are too far apart for PCR amplification. In the quote, Li expressly recognizes that the standard method of nested PCR would have worked, but Li wished to develop a new technique, ASIP PCR, for haplotyping. So when Declarant states that Li put the polymorphisms further apart in order to be able to distinguish the probes, this is not correct. Li performed the method in order to provide proof of principle (and probably to permit publication), of his novel method, ASIP PCR.

The Declarant then imposes a strained interpretation on the method of Li, stating that in his scientific opinion, "this sentence refers to the fact that the polymorphisms are separated by a distance too great for a single primer to be designed that could anneal to a region that contains multiple polymorphisms (in intron1 and exon2 here) for a single allele-specific PCR procedure (and thus requiring either nested/multiple PCRs or Li et al.'s single AISP method)." This is not consistent with the statement of Li. Li never discusses the need to design a single primer for multiple polymorphisms and this is not what allele specific PCR is all about. So this interpretation makes little sense in the

context of Li, who performs allele specific PCR with TWO different primers. If Li wished to use a single primer method, he would have said so. In the absence of such a statement, PCR, which is normally performed by two primers and allele specific PCR in particular, which Li performs with two DIFFERENT specific primers, renders Declarant's interpretation untenable because Li uses two primers and Li never tries to design a single primer for multiple polymorphisms.

The Declarant then argues the 103 rejection by failing to combine the references and provides a legal conclusion. This conclusion is not found persuasive because there is specific motivation to combine the references in the rejection. Further, when Declarant repeats the statement that the circularization of Li will not bring the polymorphisms together, Declarant is incorrectly interpreting the statement of Li that "ASIP, rather than nested PCR, can be applied to haplotyping of polymorphisms separated by a distance that is too long to be amplified by PCR (see page 361, column 1, paragraph 1)." ASIP involves forming circularized molecules and no other interpretation can be borne by the statement than that the polymorphisms that are too far apart are brought closer together to permit PCR amplification.

Response to Arguments

8. Applicant's arguments filed March 22, 2004 have been fully considered but they are not persuasive.

Applicant argues that the rejection relies on two premises that are not scientifically accurate.

First, Applicant argues that Li does not teach bringing the polymorphisms closer together. For the reasons given above in the response to the Declaration, this argument is not found persuasive. In short summary, when Li states "ASIP, rather than nested PCR, can be applied to haplotyping of polymorphisms separated by a distance that is too long to be amplified by PCR (see page 361, column 1, paragraph 1)", Li can only mean the method of ASIP should be used for distant polymorphisms. The method of ASIP requires restriction digestion and ligation of circles to bring ends closer together. So Li can only mean what Applicant incorrectly argues is not meant.

Second, Applicant argues the same untenable interpretation of Li that is argued in the Declaration. As noted above, Applicant is attempting to place the quote in a context which is not correct because it ignores and distorts the plain meaning of Li. Li would not have said that the 30-40 bases between the polymorphisms was a distance too long to be amplified by PCR when he amplified a 357 base pair fragment. Consequently, Li must have been referring, in his quote, to other polymorphisms which are too far apart for PCR amplification.

Applicant then argues that standard PCR is not commonly understood as being capable of amplifying 1000 bases. No declaration from the examiner is needed to prove this point. The cited reference of Patel shows a 1034 base pair fragment amplified by standard ARMS PCR (see figure 4). So Patel provides the evidence that standard PCR can amplify up to 1000 bases.

Applicant's citation of the opinion of the expert's on the legal conclusion of obviousness is given some weight, but does not overcome the prima facie case presented here.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

Applicant then conducts a piecemeal examination of the references, picking apart Patel by noting that it does not mention Li and Michaelos-Beloin by noting that this reference is complete in itself and that there is no motivation to combine the references. In every obviousness rejection, the references necessarily function prior to combination, or else they could not be published. So the question is not whether the methods work, but whether the combination is sufficiently prima facie obvious based upon the analysis of the Graham v John Deere factors. In the current case, there is a specific problem which is recognized by Li, and for which a solution is provided by Patel and Michaelos-Beloin. These references provide the teachings and motivations which render the claimed invention obvious.

Applicant does specifically argue that Patel would not be combined with Li because Patel teaches circularization before isolation of the target, unlike Li or

Michaelos-Beloin. This is not a patentable distinction for two reasons. First, ligation is expressly taught by Li and Li teaches performance of a ligation prior to a second PCR event. So Li expressly teaches this element and Patel is present solely to show that genomic DNA can be a source of DNA for the ASIP method of Li. Second, the claim uses the open "comprising" format. Thus, there is no required order in the claim.

Conclusion

9. All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is (571)272-0742. The examiner can normally be reached on 6:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571)272-0782. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jeffrey Fredman
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Art Unit 1637